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Effect of 24-hour blood pressure and heart rate on the prognosis of patients with reduced and midrange LVEF

Aim — Optimal combination therapy for chronic heart failure (CHF) currently implies the mandatory use of at least four classes of drugs: renin-angiotensin-aldosterone (RAAS) system inhibitors or angiotensin receptor blocker neprilysin inhibitors (ARNI); beta-adrenoblockers (BAB); mineralocorticoid receptor antagonists; and sodium-glucose cotransporter 2 inhibitors. Furthermore, many of these drugs are able to decrease blood pressure even to hypotension and alleviate tachycardia. This study focused on the relationship of 24-h blood pressure (BP) and heart rate (HR) with the prognosis for CHF patients with sinus rhythm and left ventricular ejection fraction (LVEF) <50% as well as on suggesting possible variants of safe therapy for CHF depending on the combination of studied factors.

Material and methods — Effects of clinical data, echocardiographic parameters, 24-h BP, and heart rhythm (data from 24-h BP and ECG monitors) on the prognosis of 155 patients with clinically pronounced CHF, LVEF <50%, and sinus rhythm who were followed up for 5 years after discharge from the hospital.

Results — The one-factor analysis showed that the prognosis of CHF patients was statistically significantly influenced by the more severe functional class (FC) III CHF compared to FC II, reduced LVEF (<35%), a lower 24-h systolic BP (SBP) (<103 mm Hg), the absence of hypotensive episodes in daytime, a low variability of nighttime BP (<7.5 mm Hg), a higher 24-h HR (>71 bpm vs. <60 bpm), the absence of therapy with RAAS inhibitors + BAB, and a lower body weight index. The multifactor analysis showed that more severe CHF FC, lower LVEF, and the absence of RAAS inhibitors + BAB therapy retained the influence on the prognosis. After eliminating the influencing factor of drug therapy, also a low SBP variability significantly influenced the prognosis. An additional analysis determined the following four groups of CHF patients with reduced heart systolic function according to mean 24-h HR and SBP: the largest group (38.1% of all patients) with controlled HR (≤69 bpm), preserved SBP (>103 mm Hg), and the lowest death rate of 15.3%; the group with increased HR (>69 bpm) but preserved SBP (30.3% of all patients) where the death rate was 44.7%, which was significantly higher than in the first group; the group with normal HR (≤69 bpm) but reduced SBP (≤103 mm Hg) (16.1% of patients) where the death rate was 40%, which was comparable with the second group and significantly worse than in the first group; and the group with both increased HR (>69 bpm) and reduced SBP (≤103 mm Hg) (15.5% of patients), which resulted in the maximal risk of death (70.8% of patients with CHF and LVEF <50%), which was significantly higher than in the three other groups.

Conclusion — Low SBP (including 24-h SBP with reduced variability in day- and nighttime) in combination with high HR (including by data of Holter monitoring), low LVEF, more severe clinical course of CHF, and the absence of an adequate treatment with neurohormonal modulators (RAAS inhibitors and BAB) significantly increased the risk of death. Isolating four types of FC II–III CHF with sinus rhythm and EF <50% based on the combination of HR and BP identifies patients with an unfavorable prognosis, which will help developing differentiated therapeutic approaches taking into account clinical features.

Keywords — HFrEF; HFmrEF; therapy for CHF; prognosis; SBP; BP variability

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Severe prognosis and high mortality in patients with chronic heart failure (CHF) involving reduced and mid-range left ventricular ejection fraction (LVEF <50%) persist despite improved principles of treatment [1,2]. This makes it necessary to search for informative and straightforward criteria to make the prognosis of such patients and the possibility of effective and safe treatment.

The best-possible combination therapy of CHF with systolic dysfunction currently implies the mandatory use of at least four classes of drugs: renin-angiotensin-aldosterone system (RAAS) inhibitors, such as angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACE inhibitors/ARBs) or angiotensin receptor-neprilysin inhibitors (ARNIs) and beta-blockers (BBs), and mineralocorticoid receptor antagonists (MCRAs) and sodium-glucose cotransporter 2 (SGLT-2) inhibitors, along with diuretics in congestion [for all patients with heart failure with reduced EF (HFrEF), recommendation class I. Although these same classes of drugs reduce mortality, hospitalization and are recommended for patients with heart failure with mid-range EF (HFmrEF)] [3, 4], In many cases, additional ivabradine is considered in sinus rhythm and digoxin in atrial fibrillation (AF) (recommendation class IIa for both) [3, 5].

Sequential administration was traditionally used: a RAAS inhibitor with gradual dose titration, then a BB also with dose titration, then an MCRA, and finally an SGLT-2 inhibitor [3, 4]. This regimen took up to 12 weeks, while the fastest possible simultaneous use of all four classes of drugs reduces the risk of death and rehospitalization [6].

Since many of these drugs can reduce blood pressure, as much as hypotension, and reduce the severity of tachycardia, it is important to investigate the relationship of 24-hour blood pressure (BP) and heart rate (HR) with the prognosis of CHF patients with sinus rhythm and LVEF <50%, and to suggest possible options for safe treatment of CHF depending on the combination of the factors of interest, which was the objective of this study.

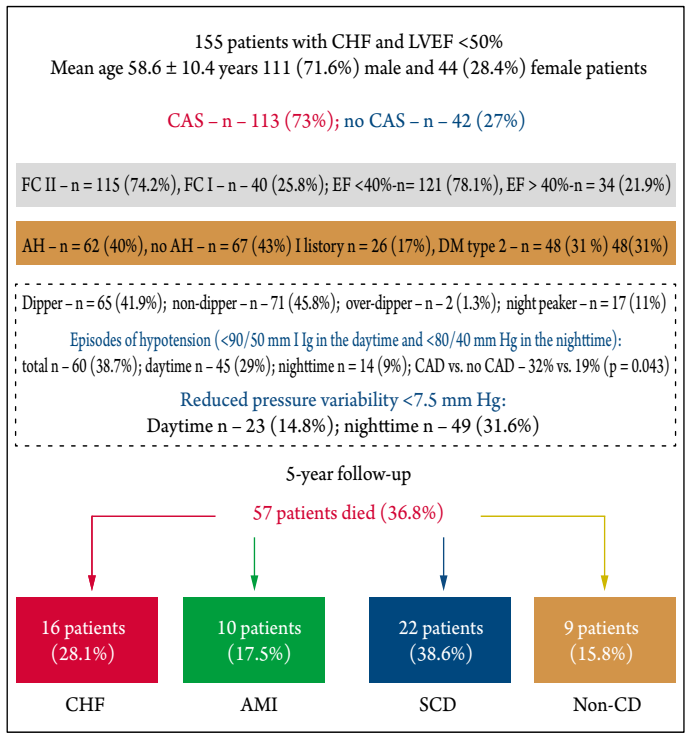
Material and Methods

The study included 155 patients with severe CI IF, LVEF <50%, and sinus rhythm, who had been treated at the Department of Myocardial Diseases and Heart Failure in A. L. Miasnikov Research Institute for Cardiology and followed up for five years after the discharge from the hospital (Figure 1). The mean age of patients was 58.6 (10.4) years; they were predominantly male (71.6%); the main cause of heart failure was CAD in 113 (73%) patients, of whom 75 (66.7%) had a history of acute myocardial infarction. The severity of CHF symptoms corresponded to functional class (FC) II in 115 (74.2%) patients and FC III in 40 (25.8%) patients; 121 (78.1%) patients had HFrEF (<40%) and 34 (21.9%) patients had HFmrEF (40–50%). Assessment of the patient's functional status included a determination of CHF FC according to the Russian Heart Failure Society (OSSN) classification and a clinical evaluation of HR and BP using the standard Korotkov method.

A two-dimensional echocardiographic examination was carried out according to the standard technique using an ATL- 5000 device (Philips, USA) with a 3.0 MHz sensor to assess hemodynamics, left ventricular end-systolic volume (LVESV), left ventricular end-diastolic volume (LVEDV) and LVEF according to the Simpson method. ECG 24-hour monitoring was performed in two leads, Vi and Vs, using a Holter monitor (Rozinn, USA). Astrocard (Meditek, Russia) software was used.

24-hour BP monitoring was carried out using AND equipment (Japan). The parameters of interest were recorded at 15-minute intervals during the daytime and every 30 minutes at night. The periods of wakefulness (daytime) and sleep (night time) were established individually during the analysis based on patient diary entries.

Figure 1. General characteristics of CHF patients examined*



CHF – chronic heart failure;
LVEF – left ventricular ejection fraction; AH – arterial hypertension;
DM – diabetes mellitus; AMI – acute myocardial infarction;
SCD – sudden cardiac death; non-CD – non-cardiac death

* – the study protocol was approved by the Ethics Committee of A.L. Miasnikov Research Institute for Cardiology. Patients signed informed consent.

The traditional parameters of the 24-hour BP profile were analyzed: mean 24-hour. daytime and nighttime systolic blood pressure (SBP), and diastolic blood pressure (DBP). Changes in BP within 24 hours were assessed individually for SBP and DBP using the following formula:

$$\text{24-hour index } (BPI_{24h} = (BP_{daytime} - BP_{nighttime}) \times 100\% BP_{daytime}.$$

BP variability ($SBPV_{daytime/nighttime}$, $DBPV_{daytime/nighttime}$) was calculated based on the standard deviation from mean BP. The normal upper level was 15/15 mm Hg for SBPV and 14/12 mm Hg for DBBP in the daytime/nighttime, respectively [7].

The hypotension time index (HTI) calculated to identify episodes of hypotension consists in the percentage of measurements exceeding the permissible decrease in BP below the threshold limit values. In this study, we used relatively low threshold limit values for SBP and DBP, which are potentially associated with hypoperfusion of vital organs: 90 mm Hg and 50 mm Ilg for SBP and DBP during the daytime; 80 mm Hg and 40 mm Hg at night, respectively.

The data were statistically analyzed using the STATISTICA 8.0 (StatSoft) software suite. The study results are presented in the tables as Me (Iq; uq) or M±SD, where Me is the median; Iq; uq is the interquartile range; M is the mean value; and SD is the standard deviation. Normal distribution was determined by the Shapiro–Wilk test. The critical value of significance was 0.05. A five-year follow-up period w as chosen to study the survival of CHF patients. The survival curves were constructed using the Kaplan–Meier method. The Cox–Mantel test was used to compare the survival curves in the two groups. In order to determine the prognostic factors affecting the survival of CHF patients, the Cox proportional hazards model with mortality risk ratio was used.

Results

Office HR was 76 [71; 82] bpm, SBP was 120 [115; 130] mm Hg, and DBP was 80 [70:80] mm Hg. AH was established in 62 (40%) patients; 26 (17%) patients had a known history of AH, i.e., AH preceded or accompanied CHF in 57% of cases. 67 (43%) of the examined patients had no AH. 24-hour BP monitoring showed a normal 24-hour SBP profile with an adequate nighttime decrease (dipper) in only 65 (41.9%) patients and with an extreme decrease (over-dipper) in 2 (1.3%) patients. An abnormal profile of 24-hour BP without a nighttime decrease (non-dipper) was observed in 71 (45.8%) patients; 17 (11%) patients had a nighttime increase in BP (night-peaker). In other words, 88 (56.8%) examined patients with CHF had a 24-hour BP profile without adequate nighttime decrease.

SBP variability was moderately reduced: in the daytime – 13 [11; 16] mm Hg; at night – 10 [8; 12] mm Hg. Adequate SBP variability turned out to be the most helpful parameter of the 24-hour BP profile in CHF. As determined by the number of hypotension episodes (<90/50 mm Hg in the daytime and <80/40 mm Hg in the nighttime), this was established in 60 (38.7%) patients within 24 hours, mainly (45 (29%) patients) in the daytime. Interestingly, the number of hypotension episodes could be associated with adequate treatment of CHF (RAAS inhibitors + BBs), which were associated with a 24-hour decrease in SBP by 9 mm Hg and DBP by 4 mm Hg; the best possible treatment was associated with the normal 24-hour BP profile more often by 11% and 7% for SBP and DBP, respectively. No significant differences were found in the parameters of HR variability. The episodes of daytime hypotension were more common in CHF of ischemic origin than in dilated cardiomyopathy (32% vs. 19%, p=0.043).

The second parameter associated with the prognosis of CHF patients was low nighttime variability of SBP (<7.5 mm Hg), which was recorded in 49 (31.6%) patients.

The characteristics of the influence of the 24-hour BP profile (trough-shaped curve with minimal risk of death in a 24-hour SBP of 121–134 mm Hg and 24-hour DBP of 78–85 mm Hg) and HR (linear dependence with minimal risk of death with 24-hour HR <60 bpm) have been already analyzed in detail [8].

57 (36.8%) patients died during the follow-up period. As seen in Figure 1, about 85% of these patients died of cardiac causes. The most common cause of death was sudden cardiac death (SCD), which occurred in 38.6% of cases; 28.2% of patients died of irreversible progression of CHF; in 17.5% of patients, exacerbation of CAD was the cause of death. However, considering the relatively small number of adverse outcomes in each subgroup and the conventional nature of the causes of death in the absence of post-mortem findings in 31 (54.4%) of 57 deceased patients, further analysis included the consolidated parameter of 'all-cause mortality'.

In this trial, we investigated the relationship between the prognosis of CHF patients with sinus rhythm along with LVEF <50% with clinical and hemodynamic parameters and 24-hour HR and SBP variability. Table 1 presents a comparative characteristic of 98 survivors with 57 patients who died during the five-year follow-up.

The groups did not differ statistically significantly in terms of age, sex, or rate of ischemic origin of the disease. The deceased patients were statistically significantly more likely to have a higher FC of heart failure and lower body mass index (BMI), while CHF was significantly less

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Table 1. Comparison of CHF patients with LVEF <50% depending on the prognosis

Parameter	Survivors, n=98	Deceased, n=57	p
Age, years	58.7 ± 10.3	57.7 ± 10.7	0.566
Sex, male	68 (69.4%)	43 (75.4%)	0.420
Origin			
• CAD • Non-CAD	71 (72.4%) 27 (27.6%)	42 (73.7%) 15 (26.3%)	0.867
• CHF FC II • CHF FC III	82 (83.6%) 16 (16.4%)	33 (57.9%) 24 (42.1%)	0.002
• AH • Non-AH • History of AH	48 (49%) 33 (33.7%) 17 (17.3%)	14 (24.6%) 34 (59.6%) 9 (15.8%)	0.004
SBP, mm Hg	122 [115;130]	116 [105;130]	0.009
DBP, mm Hg	80 [72;80]	78 [70;80]	>0.05
HR, 24-hour	64 [58;72]	67 [60;78]	0.035
11R <median 66 bpm	56 (57.1%)	22 (38.6%)	0.027
BM1, kg/nr	28.3 [26.1;31.6]	27.1 [25.0;29.4]	0.028
Normal 24 h SBPV index	45 (45.9%)	15 (26.3%)	0.042
Systolic hypertension daytime episodes (<90/50 mm 1 Ig)	36 (36.7%)	9 (15.8%)	0.008
Systolic hypertension nighttime episodes (<80/40 min 11g)	10 (10.2%)	4 (7.0%)	0.505
SBPV nighttime <7.5%	10 (17.5%)	39 (39.8%)	0.013
Mean nighttime SBP	113 (102-122)	112 (103-124)	>0.05
LVEF, %	36 [30;42]	29 [25;36]	<0.001
LVEF <40%	69 (70.4%)	52 (91.2%)	0.004
LVEDV, mL	211 [162;254]	255 [213;289]	<0.001
LVESV, mL	136 [100;178]	180 [136;213]	<0.001
ACE inhibitors/ARBs, n (%)	83 (84.7%)	38 (66.7%)	0.011
Beta-blockers, %	80 (81.6%)	45 (78.9%)	0.683
MCRA, n (%)	40 (40.8%)	18 (33.3%)	0.252
Digoxin, %	23 (23.5%)	14 (24.6%)	0.878

CHF FC – functional class of chronic heart failure according to the classification of the New York Heart Association; AH – arterial hypertension; DBP – diastolic blood pressure; HR – heart rate; BML body mass index; SBP – systolic blood pressure; SBPV – systolic blood pressure variability; LVEF – left ventricular ejection fraction; LVEDV – left ventricular end-diastolic volume; LVESV – left ventricular end-systolic volume; ACE – angiotensin-converting enzyme; ARB – angiotensin 11 receptor blocker; BB – beta-blocker; MCRA – mineralocorticoid receptor antagonist.

frequently associated with AH in such patients. In this group, SBP was lower (A=6 mm Hg, p=0.009), but HR was higher (A=bpm, p=0.035). Survivors were more likely to have normal 24-hour SBP variability index (p=0.042). Episodes of daytime hypotension (<90/50 mm Hg), being a marker of preserved BP variability, were statistically significantly more frequent in survivors (p=0.008); decreased nighttime SBP variability (<7.5 mm Hg) was also frequent in deceased patients. Among 45 patients who had episodes of daytime hypotension, 93.3% received RAAS inhibitors + BBs; only 71.8% of patients without such a decrease in BP in the daytime received the mentioned treatment (p=0.032). There were no statistically significant differences in the administration of other drug classes.

The median LVEF was 35.3 (Q25; Q75)% in the study group. HFrEF (EF <40%) was established in 70.4% of survivors and 91.2% of deceased patients (p=0.004). The differences in mean LVEF between the groups of survivors and deceased patients were statistically significant (36% vs. 29%, respectively); the same was true for LV volumes, which were significantly higher in the deceased group.

RAAS inhibitors were used more rarely in the group of deceased patients (38/57 (66.7%) patients) than in survivors (83/98 (84.7%) patients, p=0.011); the frequency of using BBs, MCRAs, and digoxin did not differ significantly. Table 2 shows the main characteristics statistically significantly related to the prognosis of patients with HFrEF and HFmrEF in the study group in the univariate analysis.

The deteriorated prognosis of patients was statistically significant with more severe clinical manifestations of CHF (FC III), a decrease in EF less than 35%, an increase in 24-hour HR more than 71 bpm versus HR of less than 60 bpm, and a reduction in office SBP less than 115 mm Hg and 24-hour HR <103 mm Hg.

Increased BMI (the so-called 'obesity paradox' in CHF) and AH at the time of examination or history of AH were the factors that statistically significantly improved the prognosis of patients with CHF FC II – III and LVEF <50%.

Table 2. Univariate analysis of the influence of various factors on the risk of death in CHF with LVEF <50% and sinus rhythm

Parameters	OR	95% Cl	p
FC III vs. FC 11	2.76	1.44-4.30	0.0001
LVEF <35.3 % vs. >35.3 %	3.57	2.17-5.88	0.0001
BMI >31.4 g/m² vs. <25.9 g/m²*	0.44	0.31-0.64	0.0002
HR >71 bpm vs <60 bpm*	1.50	1.15-1.97	0.002
SBP <115 mm Hg vs. >115 mm Hg	2.17	1.38-3.44	0.004
SBP 24 h <103 mm Hg vs. >115 mm Hg	2.16	1.11-4.17	0.04
AH + history of AH vs. no Ail	0.34	0.17-0.67	0.0019
SBPV nighttime >15 mm Hg vs. <7.5 mm Hg*	0.24	0.08-0.69	0.027
Systolic hypertension daytime episodes (<90/50 mm Hg)	0.46	0.25-0.86	0.042
No ACE inhibitor + BB versus ACE inhibitor + BB	2.88	1.92-3.76	0.013

AH – arterial hypertension; SBPV – systolic blood pressure variability; OR – odds ratio; CI – confidence interval.
* – upper tertile versus lower tertile.

Table 3. Multivariate Cox analysis exploring factors influencing the prognosis of CHF patients with LVEF <50% and sinus rhythm

Parameter	OR	95%	p
CHF FC III	2.28	1.43–3.64	0.004
LVEF lower than median (<35.3%)	2.11	1.24–3.96	0.021
No ACE inhibitor + BB	2.41	1.46–3.96	0.004
No episodes of systolic hypotension in the daytime	1.99	1.05–3.77	0.077
Nighttime SBPV <7.5 mm Hg	1.79	1.06–3.03	0.064

OR – odds ratio; CI – confidence interval; FC – functional class; CHF – chronic heart failure; ACE – angiotensinconverting enzyme; BB – beta-blocker; SBP – systolic blood pressure.

It is significant that two preserved normal BP variability parameters were also associated with better survival in patients with HFrEF and HFmrEF. The episodes of hypotension <90/50 mm Hg in the daytime during the best possible treatment with a combination of RAAS inhibitors + BBs were reported in 45 (29%) patients, characterized by a 54% reduction in the risk of death (p=0.042). Preserved nighttime BP variability >15 mm IIg reported in 36 patients, unlike reduced SBP variability <7.5 mm Hg in 49 patients, was accompanied by a 76% decrease in the risk of death (p=0.027). This resembles the relationship of higher HR variability with a lower risk of death in patients with CHF, which was analyzed in detail in our recent study [9]. The corresponding associations of SBP variability with the survival rate of Cl IF patients with LVEF <50% are provided in Figure 2-1 and Figure 2-2. It is also of interest to assess the combination of clinical manifestations of CHF (CI IF FCs) with preserved BP variability and patient survival. The chances of staying alive in CHF FC II combined with episodes of daytime hypotension are 9.2 times as high as in CHF FC III and 'monotonic' daytime hypotension (Figure 2-3). The combination of CHF FC III and low nighttime SBP variability (<7.5 mm Hg) is associated with a higher risk of death (OR 3.9) than the combination of CHF FC II and preserved nighttime SBP variability (>15 mm Hg; Figures 2-4). The multivariate Cox analysis established five main parameters retaining their influence on the prognosis of patients with CHF FC II-III, sinus rhythm, and LVEF <50%. The data are given in Table 3.

Three of them retained a statistically significant relationship with the prognosis: a more severe course of CHF (FC III), low LVEF, and a lack of the best possible treatment with ACE inhibitors and BBs. The parameters of low-pressure variability were only likely to be associated with the prognosis of patients, and that tendency had no statistically significant differences.

Given that one of the key parameters of influence on the prognosis turned out to be 'man-made', i.e., a failure to comply with the treatment of CHF and the absence of best possible treatment with RAAS inhibitors + BBs, we excluded this from the second Cox model. The results are presented in Table 4.

In this case, low BP variability (no decrease in BP in the daytime and a decrease in the nighttime SBP variability less than 7.5 mm Hg), along with the clinical severity of the disease (CHF III FC) and LVEF <35%, turned out to be factors that significantly worsen the prognosis of HFrEF and HFmrEF patients.

Figure 3 shows the effect of the combination of all three factors on the survival rate of patients with CHF and LVEF <50% during the long-term follow-up. The decrease in the death risk ratio in patients with CHF FC II, EF >35%, and preserved BP variability (adequate decrease in the daytime) is 66% (p=0.0034), i.e., almost three times as low as in more severe CHF FC III, low LVEF <35%, and low BP variability.

As shown in Table 2, increased 24-hour HR and reduced 24-hour BP had a negative effect on the survival of patients with CHF in the univariate prognostic analysis. On the other hand, most of the drugs recommended for the treatment of this syndrome affect BP and HR; moreover, the indications for their use depend on the initial levels of these parameters. Therefore, we conducted a separate analysis of the combined effect of 24-hour HR and BP on the prognosis of patients with HFrEF and HFmrEF.

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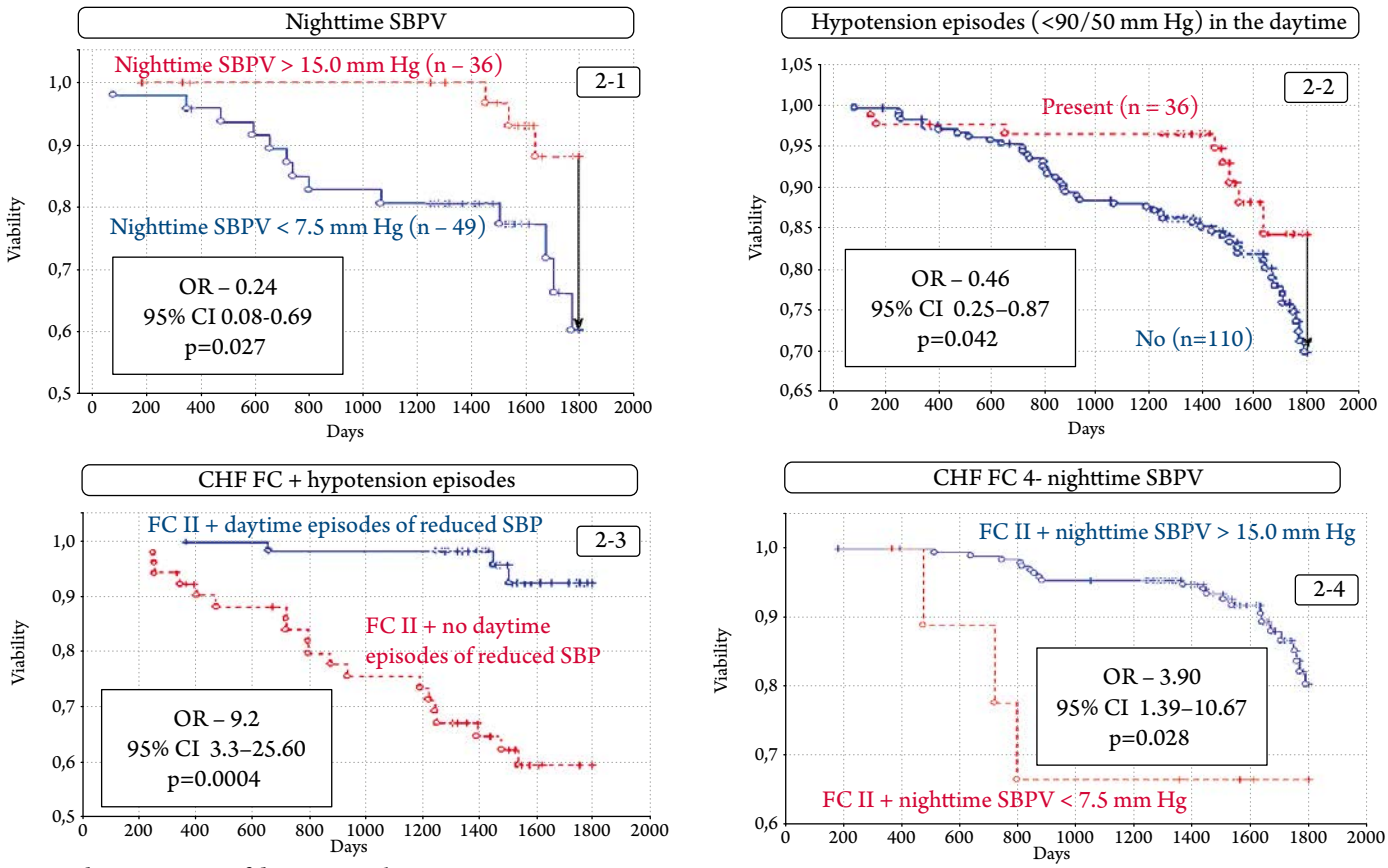
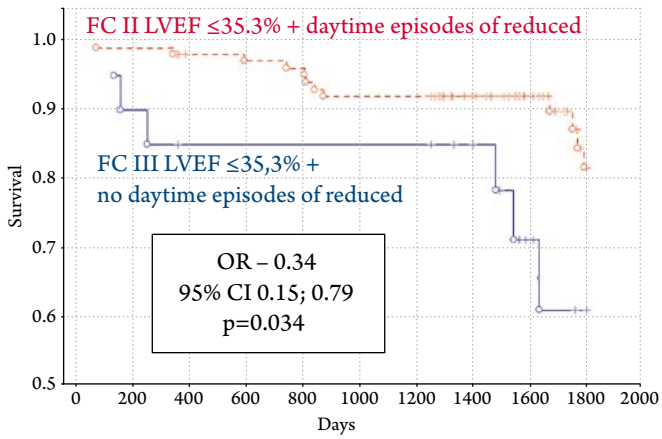
Figure 2. Survival of CHF patients with LVEF <50% and sinus rhythm depending on the nighttime SBPV (2-1), daytime BP in the form of hypotension episodes (2-2), and in combination with CHF FC (2-3 and 2-4)



OR – risk ratio; CI – confidence interval;
SBP – systolic blood pressure; FC – functional class according to the New York Heart Association classification; CHF – chronic heart failure.

Figure 3. Effects of the combination of CHF FC, LVEF, and BP variability (by the presence of daytime episodes of reduced SBP (< 90 mm Hg) on the survival of CHF patients



OR – odds ratio; CI – confidence interval;
LVEF – left ventricular ejection fraction; SBP – systolic blood pressure; FC – functional class according to the New York Heart Association classification; CHF – chronic heart failure.

Figure 4 shows survival curves depending on tertiles of 24-hour HR (upper tertile versus lower tertile) and median 24-hour SBP. As seen in this figure, an increase in 24-hour HR from 60 bpm to 71 bpm with a 24-hour SBP higher than the median (>103 mm Hg) increases the risk of death 1.5-fold (p=0.006). At the same time, a similar increase in 24-hour HR 60 bpm to 71 bpm with a 24-hour SBP lower than the median (>103 mm Hg) increases the risk of death 3.9-fold (p=0.037).

The best survival rate of CHF patients was established with lower 24-hour HR (<60 bpm) and preserved 24-hour SBP higher than the median (>103 mm Hg). The worst survival was observed in the subgroup of patients with high 24-hour HR (>71 bpm) and low 24-hour SBP (≤ 103 mm Hg). Since the difference in the risk of death was 5.6-fold between these groups (p=0.009), it can be concluded that the survival rate of CHF patients is most severely affected by a combination of tachycardia with hypotension.

Given this fact, we divided the examined patients with CHF FC II – III and EF <50% into four groups according to median 24-hour HR and median 24-hour SBP (Figure 5).

The group with 24-hour HR slower than the median (<69 bpm) and preserved 24-hour SBP (>103 nun Hg) was the most numerous and included 38.1% of all patients. The same group of patients had the most favorable prognosis. The mortality rate was 15.3%.

The group with 24-hour HR slower than the median (<69 bpm) and preserved 24-hour SBP (>103 mm Hg) was the second most numerous and included 30.3% of all patients. The mortality rate of 44.7% was significantly higher than in the previous group (p=0.014).

The third most numerous group included 16.1% of all patients who had 24-hour HR slower than the median (<69 bpm) and decreased 24-hour SBP (<103 mm Hg); the mortality rate was 40% in this group, which was comparable to the second group. The differences in the rate of deaths compared with the first group were statistically significant (p=0.048).

Thus, both an increase in 24-hour HR higher than the median (up to 44.7%) and a decrease in 24-hour SBP lower than the median (up to 40.0%) increase the mortality of CHF patients approximately equally.

The smallest group of patients (15.5%) had increased 24-hour HR (>69 bpm) and 24-hour BP lower than the median (<103 mm Hg), in which mortality was the highest (70.8 %). Thus, a simultaneous increase in HR and a decrease in BP worsen the prognosis of CHF patients as much as possible.

Thus, it may be helpful to identify subgroups of patients with different baseline HR and SBP values to choose between different treatment options depending on the effects of the recommended drugs for the treatment of CHF on these parameters.

Discussion

The main objective of this study was to critically assess the effect of IIR and BP on the prognosis of CHF patients with sinus rhythm and reduced or mid-range LVEF. The methods of 24-hour monitoring of HR and BP were used in a selected group of patients to assess the optimal contribution of these parameters.

57 (36%) of the 155 patients with CHF and LVEF <50% died during the five-year follow-up period. The first stage of the univariate analysis confirmed the role of two key factors influencing the prognosis of patients with reduced LVEF: the severity of CHF (FC III versus FC II), which significantly increased the risk of death 2.76 times (p <0.0001); the degree of heart remodeling characterized by LVEF lower than the median (<35.3%) increased the risk of death by 3.57 times (p <0.0001).

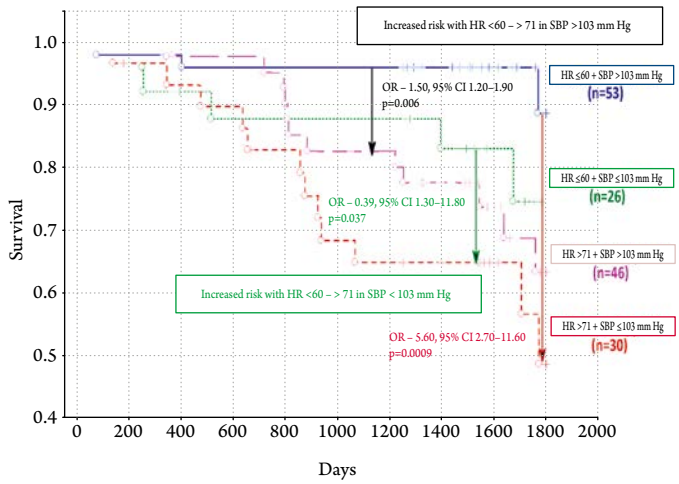
A history of AH or increased BP during the examination was accompanied by a significant decrease in the risk of unfavorable prognosis by 66% (p=0.002). Conversely, hypotension (office SBP <115 mm Hg and 24-hour BP <103 mm Hg) was a predictor of poor prognosis, significantly increasing the risk of death by 2.17 times (p=0.04) [10]. Moreover, tachycardia in the form of increased mean 24-hour HR of more than 71 bpm (upper tertile) compared to HR of

Table 4. Multivariate Cox analysis exploring factors significantly influencing the prognosis of CHF patients with LVEF <50% with the treatment effect excluded

Parameter	OR	95% CI	p
CHF FC (III)	2.25	1.41–3.59	0.004
LVEF lower than median (<35.3%)	2.74	1.63–4.63	0.001
No episodes of systolic hypotension in the daytime	2.37	1.26–4.45	0.024
Nighttime SBPV <7.5 mm Hg	1.92	1.14–3.23	0.039

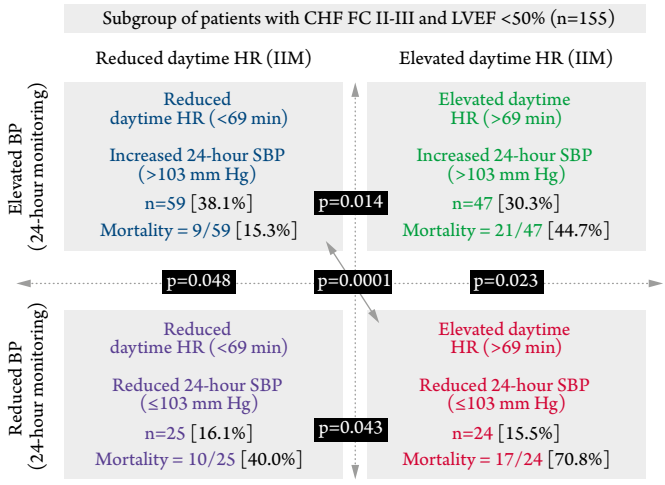
OR – odds ratio; CI – confidence interval;
FC – functional class; CHF – chronic heart failure.

Figure 4. Survival of patients with CHF and LVEF ejection fraction depending on 24-hour HR and 24-hour SBP



OR – odds ratio; CI – confidence interval;
HR – heart rate; SBP – systolic blood pressure

Figure 5. Division of patients with CHF FC II-III and LVEF <50% into groups depending on the median HR and 24-hour SBP



CHF – chronic heart failure; HM – Holter monitoring;
HR – heart rate; SBP – systolic blood pressure.

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less than 60 bpm (lower tertile) also negatively affected the prognosis of patients, albeit to a relatively lesser extent than hypotension. The risk of death in patients with HFrEF and HFmrEF increased 1.5 times with increased 24-hour HR of more than 71 bpm (p=0.002).

It is a well-known fact that patients with severe CHF (FC II-III) have 'monotonous tachycardia' with decreased HR variability in a significant imbalance of neurohormones during chronic hyperactivation of the RAAS and the sympathetic-adrenal system (SAS) [11, 12]. It has been shown recently in the ONYX trial that decreased HR variability is correlated with the risk of life-threatening ventricular arrhythmias [9]. This is a possible additional factor of the negative impact of low HR variability on the prognosis of CHF patients [13].

There is much less data on BP variability in patients with CHF. We have demonstrated that low SBP variability and its decrease below the median – the so-called 'monotonic hypotension' – are also associated with a worse prognosis of patients with HFrEF (<50%). Conversely, preserved SBP variability reduced the risk of death in patients with severe CHF. At the same time, the prognosis was statistically significantly related with episodes of daytime hypotension (SBP <90/50 mm Hg), which were more frequent during the best-possible treatment with an ACE inhibitor + BB combination and associated with a 54% decrease in the risk of death (p=0.042), and with preserved nighttime variability (BP >15%, upper tertile) versus decreased nighttime variability (<7.5 mm Hg, lower tertile), associated with a 76% decreased in the risk of death (p=0.027).

In the multivariate Cox analysis, only three parameters (higher CHF FC, lower EF, and lack of adequate treatment with neurohormonal modulators (ACE inhibitors + BBs) worsened the prognosis of CHF patients to a statistically significant extent. At the same time, the correlation of the the daytime and nighttime SBP variability parameters with the prognosis was lost (only the trend continued).

When the factor of treatment associated with a low level of training of doctors and poor treatment compliance was excluded from the analysis, both SBP variability parameters of interest again demonstrated a statistical relationship with the prognosis of CHF patients. Thus, the combination of low nighttime SBP variability (<7.5 mm Hg) with more severe CHF FC III increased 3.9-fold the risk of death in CHF patients with LVEF <50% (p <0.0001), while the combination of low daytime SBP variability (no episodes of hypotension) with more severe CHF III FC increased 9.2-fold the likelihood of unfavorable prognosis (p <0.0001).

At the final stage of the study, we evaluated the combined effect of 24-hour HR and 24-hour SBP on the prognosis of patients with HFrEF and HFmrEF. This is of fundamental importance since the clinical measurement of HR and BP used in routine practice is highly variable, since depending not only on the characteristics of CHF. These parameters can be affected by the patient's morale and psychological state, the time of day, the weather, and even the presence of medical staff. Therefore, only 24-hour monitoring of HR and BP can comprehensively explain the effect of these indicators on the prognosis of patients with CHF and systolic dysfunction.

In patients with 24-hour SBP higher than the median (>103 mm Hg), an increase in 24-hour HR from less than 60 bpm to more than 71 bpm (lower and upper tertiles, respectively) was accompanied by a 1.5-fold increase in the risk of death (p=0.006), while the same increase in HR in patients with 24-hour SBP lower than the median (<103 mm Hg) increased the risk of death by as much as 3.9 times (p=0.037). Patients with CHF and HR >71 bpm and a simultaneous decrease in 24-hour SBP <103 mm Hg are more likely to die (5.6 times, p=0.0009) than patients with 24-hour HR less than 60 bpm and 24-hour SBP higher than the median.

The analysis, which was conveniently carried out in 4 groups of patients with CHF FC II-III and LVEF <50%, unequivocally confirmed our assumptions.

Patients with optimal 24-hour BP (>103 mm Hg) and normal mean 24-hour HR (<69 bpm), which is about 40% of all patients examined, have a better prognosis (mortality 15.3%). The drugs that reduce both BP and HR can be simultaneously administered in such patients. In this case, the treatment algorithm implying the simultaneous administration of all four drugs that improve the prognosis of CHF patients can be recommended: ARNIs with BBs, MCRAs, and SGLT-2 inhibitors with simultaneous gradual titration of ARM and BB doses. If HR is not adequately controlled, ivabradine can be additionally administered to patients with HFrEF.

The mortality rate is as high as 40% in patients with preserved 24-hour SBP (>103 mm Hg) and increased mean 24-hour HR >69 bpm (about 30% of all patients); the treatment algorithm should imply active titration of BB doses (if necessary, in combination with ivabradine). SGLT-2 inhibitors and MCRAs can also be administered simultaneously. ARNIs or ACE inhibitors should be administered with caution and slow, gradual dose titration.

In patients with 24-hour SBP lower than the median (<103 mm Hg; 31.6%), the mortality rate was 40% with mean 24-hour HR<69 bpm, while the highest mortality rate was 70.8% with low BP and increased (>69 bpm) mean 24-hour HR. While ARNIs are not indicated in these groups, treatment with ACE inhibitors (and especially titration of their doses) may be complicated by a progressive decrease in BP. If the administration of ACE is complicated, it is advisable to start treating patients with mean 24-hour HR<69 bpm and mean 24-hour SBP <103 mm Hg with a combination of

SGLT-2 inhibitors and MCRAs with the subsequent gradual addition of ACE inhibitors and BBs.

The main problem in the most challenging subgroup with tachycardia and hypotension is to decrease HR; this can be accompanied by a relative increase in BP and an extension of the 'window of opportunities' for the successful administration of other drugs recommended for successful treatment of CHF. As shown in the CIBIS-3 trial, initiating small doses of BBs, which is most effective in reduced LVEF <28%, can be recommended in this case to prevent a decrease in BP [14]. However, since even low doses of BBs can lower BP in decompensated patients, it becomes difficult to titrate their doses [15]. In these cases, ivabradine can be effectively used to control HR without lowering BP [16]; moreover, BBs combined with ivabradine can be titrated faster to achieve higher appropriate doses [17], At the second stage, SGLT-2 inhibitors and MCRAs are added to ivabradine and BBs, while RAAS inhibitors are slowly titrated. It should be noted that a BP decrease in decompensated LV is favorable for decreasing the post-load with gradually regressing heart remodeling; this, along with HR control, is eventually accompanied by the recovery of LV wall motion and pumping function, and the normalization of BP.

Conclusion

In addition to reduced left ventricular ejection fraction, more severe clinical course of chronic heart failure, and lack of the best possible treatment with neurohormonal modulators (renin-angiotensin-aldosterone system inhibitors and beta-blockers), low systolic blood pressure (including 24-hour value with reduced variability in the daytime and nighttime) in combination with high heart rate (including according to Holter monitoring) contributes significantly to the risk of death.

The identification of patients with poor prognosis by isolating the four types of chronic heart failure functional class II-III with sinus rhythm and ejection fraction <50% based on the combination of heart rate and blood pressure will help to develop differentiated treatment approaches that take clinical features into account.

Limitations

The small size of the trial, lack of information on changes in the treatment during the follow-up of patients.

No conflict of interest is reported.

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